

Hepatectomy of segment 4b and 5 with extrahepatic bile duct resection for pT2 gallbladder carcinoma is valid: a single-institution result

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Abstract The results of surgical treatment for T2 gallbladder carcinoma are equivocal, while the precise preoperative TNM staging and localization of gallbladder carcinoma are difficult. The aim of this study was to report the validity of segment 4b and 5 (S4b+5) hepatectomy with extrahepatic bile duct resection for these tumors. We reviewed 30 patients with pT2 gallbladder cancer who underwent S4b+5 hepatectomy with extrahepatic bile duct resection. The median number of lymph nodes retrieved in the S4b+5 hepatectomy group was 11 (0–23) nodes, and lymph node metastasis was observed in 9 of 30 (30 %) cases. Although all surgical margins were macroscopically negative, 4 of the 30 patients (13 %) had pathologically positive margins. The overall survival rate of patients was 85.1 % at 5 years. Of the 30 patients with S4b+5 hepatectomy, surgical margin alone was analyzed as a prognostic factor in univariate and multivariate analysis. The survival rate was comparable between the tumor on the hepatic side and peritoneal side ($P = 0.856$). Nine patients with additional S4b+5 hepatectomy after simple cholecystectomy because of incidental diagnosis of gallbladder cancer also had comparable survival compared to the remaining 21 patients with simultaneous S4b+5 hepatectomy ($P = 0.624$). S4b+5 hepatectomy with extrahepatic bile duct resection could be good treatment modality for T2 gallbladder cancers because precise preoperative diagnosis

of tumor depth, location, and lymph node metastasis for these tumors is difficult.

Keywords Hepatectomy of segment 4b and 5 · Hepatectomy of segment 4a and 5 · Extrahepatic bile duct resection · T2 gallbladder carcinoma · Cholecystectomy

Introduction

The results of surgical treatment methods for T2 gallbladder carcinoma are equivocal. Pathologically, T2 disease (pT2), which invades perimuscular connective tissue and does not extend beyond the serosa or into the liver [1, 2], may be cured after appropriate surgical resection [3]. Recently, two multicentered studies compared segment 4b and 5 (S4b+5) hepatectomies with liver bed resection for these tumors [2, 4]. Although these studies concluded that these two procedures showed comparable survival, only half of the patients underwent extrahepatic bile duct resection in one of the studies and the data were unknown in the other. In contrast, lymph node dissection and whether to perform extrahepatic bile duct resection remain controversial [5]. Recent reports have shown that there was no difference in survival between the resection and non-resection groups. However, most of the pT2 cases in their cohort received surgery without liver resection or with liver wedge resection.

Precise preoperative TNM staging for gallbladder carcinoma is difficult [3]. The preoperative diagnosis of tumor invasion was correct in only half of the cases, and this rate was lower in patients with pT1 and pT2 disease. The preoperative detection of lymph node metastasis was more difficult. Positive nodes were correctly diagnosed in only one quarter of node-positive cases. Furthermore, a recent

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multicenter study showed that tumor location, i.e., hepatic or peritoneal side, affected survival rates [6]. However, it is well known that superficial extension was often detected in biliary tumors, though it is difficult to diagnose it preoperatively [7–10].

Therefore, S4b+5 hepatectomy with extrahepatic bile duct resection could be useful for pT2 gallbladder cancers because this procedure includes adequate liver resection and lymph node dissection. Here, we analyzed the clinical and histopathologic features of consecutive patients with pT2 tumors treated by resection at a single institution. The aim of this study was to report the validity of S4b+5 hepatectomy with extrahepatic bile duct resection for these tumors.

Methods

Patient selection

We identified 47 patients who underwent resection of pT2 gallbladder carcinomas from 1994 to 2013 in the Department of Surgery, Ogaki Municipal Hospital. To evaluate S4b+5 hepatectomy with extrahepatic bile duct resection, we excluded 15 patients who underwent cholecystectomy alone and two patients who underwent right hemihepatectomy. The remaining 30 patients who underwent macroscopically curative resections comprised the final cohort and were studied in detail. Of note, no patients received adjuvant chemotherapy. From the medical records, we surveyed these patients retrospectively and reviewed the histologic slides. The institutional review board of Ogaki Municipal Hospital approved the study protocol.

Although surgical approaches, i.e., cholecystectomy and hepatectomy, for gallbladder cancer varied among the different surgeon, a fundamental institutional strategy was established in recent years. According to our policy, for cancers more than a clinical grade of T2, S4b+5 hepatectomy with extrahepatic bile duct resection has primary been performed [11, 12]. Pancreatoduodenectomy was added for advanced cancers that had pancreatic lymph node metastasis. The extent of liver resection was determined based on the pre- or intra-operative findings (i.e., biliary and hepatic invasion). For patients who had an incidental diagnosis of gallbladder cancer after simple cholecystectomy for other benign causes, additional hepatectomy of S4b+5 with extrahepatic bile duct resection was considered.

Pathological assessment

For all 30 patients, surgical specimens of gallbladder carcinoma were cut at intervals of 0.5–1.0 cm, resulting in

10–40 blocks for each patient. We macroscopically confirmed the spread of the tumors, and cut around them as much as possible. The pathological findings were described using the TNM Classification of Malignant Tumors by the International Union Against Cancer (7th edition, 2009) [1].

All tumors were confirmed pathologically as T2, which invades perimuscular connective tissue and does not extend beyond the serosa or into the liver. The main location of the tumor, i.e., hepatic or peritoneal side, was defined as follows: T2 tumors were classified as being located on the peritoneal side when the tumor infiltrated only the free serosal side of the gallbladder and on the hepatic side when at least part of a tumor infiltrated the part of the gallbladder wall attached to the liver [6]. For patients who underwent cholecystectomy, whether the tumor was outlined by serosa defines the location of peritoneal or hepatic side.

Follow-up and statistical analysis

Patient survival was determined as the interval from the time of surgery to the time of death or the most recent follow-up. The median follow-up periods were 88.7 months in patients who underwent hepatectomy of S4b+5. None died of postoperative complications.

Measurement values for continuous variables are expressed as the median (range) or mean \pm standard deviation. Postoperative survival was calculated using the Kaplan–Meier method. Differences in survival curves were compared using the log rank test. The results were considered statistically significant if the *P* value was <0.05 . All calculations were performed using the IBM SPSS Statistics 16 software package (IBM Japan Inc., Tokyo, Japan).

Results

Thirty patients who underwent hepatectomy of S4b+5 were retrieved from the entire cohort. Notably, extrahepatic bile duct resection was performed in all 30 cases. Nine of the 30 patients (30 %) had an incidental diagnosis of gallbladder cancer after simple cholecystectomy; therefore, additional S4b+5 hepatectomy was performed. Median time between cholecystectomy and additional hepatectomy was 40 (20–58) days.

Table 1 shows the clinicopathological features of pT2 gallbladder cancer. The median age was 71 (52–84), and there were 8 men and 22 women in the group. One of 30 cases (3 %) underwent combined pancreatoduodenectomy for peripancreatic lymph node metastasis. The median operative time was 247 (170–438) min, and the median blood loss was 512 (100–1400) ml. The major complications, which were defined by Clavien-Dindo Grade ≥ 3 [13],

Table 1 Characteristics of pT2 gallbladder cancer

	S4b+5 Hx with BDR (<i>n</i> = 30)
Age	71 (52–84)
Sex	
Men	8 (27 %)
Women	22 (73 %)
Combined resection	
Extrahepatic bile duct	30 (100 %)
Pancreatoduodenectomy	1 (3 %)
Operative time (min)	247 (170–438)
Blood loss (ml)	512 (100–1400)
With complication (\geq Grade III [13])	6 (20 %)
Mortality	0
Location	
Hepatic side	22 (73 %)
Peritoneal side	8 (27 %)
Number of lymph nodes retrieved	11 (0–23)
Histological type	
pap	6 (20 %)
tub	24 (80 %)
Lymphovascular and neural invasion	
ly (present)	17 (57 %)
v (present)	6 (20 %)
pn (present)	10 (33 %)
Lymph node metastasis	
Regional (present)	9 (30 %)
Para-aortic (present)	1 (3 %)
Surgical margin	
Negative	26 (87 %)
Pathologically positive	4 (13 %)

S4b+5 Hx with BDR: Segment 4b and 5 hepatectomy with extrahepatic bile duct resection

Expressed as *N* (%) except for age, operative time, blood loss and number of lymph nodes retrieved [median (range)]

pap Papillary adenocarcinoma, *tub* Tubular adenocarcinoma, *ly* Lymphatic invasion, *v* Vascular invasion, *pn* Neural invasion

occurred in 6 patients (20 %), and no mortality was observed. Bile leakage was the most common complication in the group, i.e., 4 of 6 cases.

The median number of lymph nodes retrieved in the S4b+5 hepatectomy group was 11 (0–23) nodes. Regarding the location of the tumor, 22 patients (73 %) had hepatic-side tumors and 8 (27 %) had peritoneal-side tumors. Regional and para-aortic lymph node metastasis was observed in 9 (30 %) and 1 (3 %) cases, respectively. Although all surgical margins were macroscopically negative, 4 of the 30 patients (13 %) had pathologically positive margins. The radial bile duct margin [14] and the distal bile duct margin were positive for cancer in 3 and 1 patients, respectively.

The overall survival rate of patients who underwent S4b+5 hepatectomy was 89.5 % at 3 years, and 85.1 % at 5 years (Fig. 1). Of the 30 patients in the S4b+5 hepatectomy group, surgical margin alone was analyzed as a prognostic factor in univariate and multivariate analyses, despite the small population (Fig. 2). Meanwhile, location of tumor, which was reported as a prognostic factor in T2 gallbladder carcinoma [6], did not affect survival, and the survival rate was comparable between the tumors on the hepatic and peritoneal sides ($P = 0.856$; Fig. 3). Nine patients, who underwent additional S4b+5 hepatectomy after simple cholecystectomy because of incidental diagnosis of gallbladder cancer, also had survival that was comparable with the remaining 21 patients ($P = 0.624$; Fig. 4).

Discussion

The current surgical result of S4b+5 hepatectomy for pT2 gallbladder cancers showed superior survival, compared with previously reported cases [2, 4]. Table 2 shows the comparison of clinicopathologic features between our series and multicentered studies. Only two study groups, The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) and The Japanese Society of Biliary Surgery (JSBS), surveyed S4b+5 hepatectomy for gallbladder cancers. The former group study included 30 patients with pathologically T2, N0 gallbladder cancers treated with S4b+5 hepatectomy, and the latter consisted of 58 and 30 patients with pathologically T2 cancers in hepatic and peritoneal site, respectively. The survival rates in our study were comparable to those of peritoneal-side cases in the JSBS series, although tumors located on the peritoneal side are supposed to have better survival [6]. Our series (85.1 % at 5 years) and the JSBS series located on the peritoneal site (86 %) had better survival rates compared to the JSHPBS series (65.9 %) and the JSBS series located on the hepatic site (72 %). Of note, the cohort of JSHPBS had no lymph node metastasis because of their selection criteria, while the rate of lymph node metastasis was similar among the remaining three groups (our series; 30 %, JSBS hepatic site; 28 %, and JSBS peritoneal site; 23 %). One possible reason for this might be that extrahepatic bile duct resection was performed for all S4b+5 hepatectomy cases in our series, while it was only performed for half of the cases in the multicentered studies. Lymph node metastasis and perineural invasion in patients with gallbladder carcinoma are strong indicators of poor prognosis [12, 15–17]. Removal of extrahepatic bile duct enables us to eradicate the regional nodes completely and clear the connective tissue in the hepatoduodenal ligament [15]. Therefore, the survival difference in S4b+5 hepatectomy may be due to

Fig. 1 Survival rates for patients with pT2 gallbladder carcinoma who underwent segment 4b and 5 hepatectomy (S4b+5 Hx)

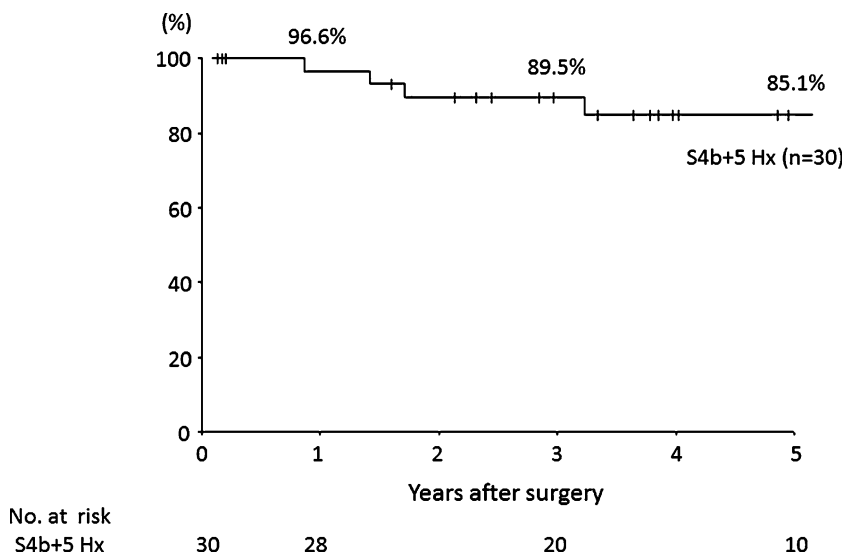


Fig. 2 Survival rates for patients with pT2 gallbladder carcinoma who underwent segment 4b and 5 hepatectomy (S4b+5 Hx) with negative and pathologically positive surgical margins. A log rank test

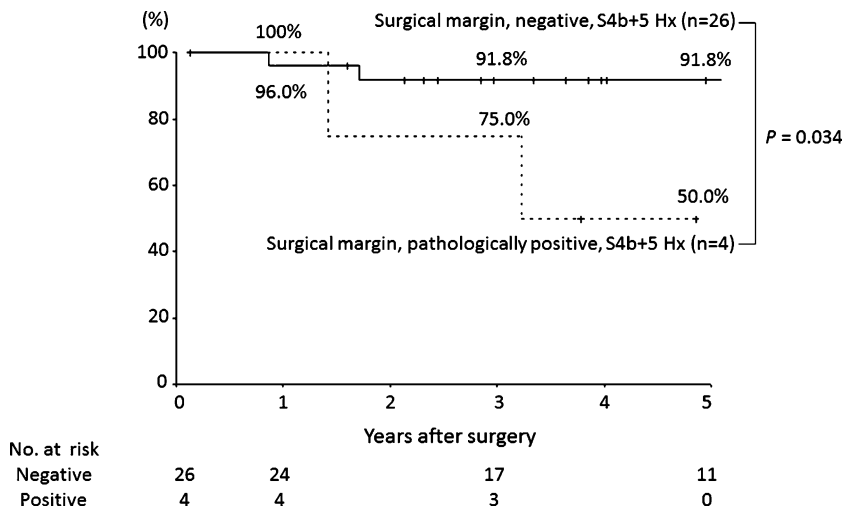


Fig. 3 Survival rates for patients with pT2 gallbladder carcinoma located in hepatic and peritoneal side who underwent segment 4b and 5 hepatectomy (S4b+5 Hx). A log rank test

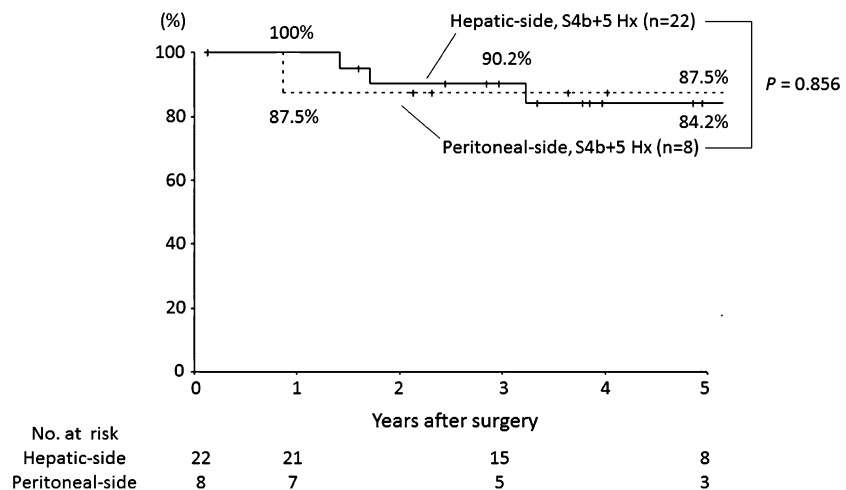


Fig. 4 Survival rates for patients with pT2 gallbladder carcinoma who underwent additional segment 4b and 5 hepatectomy (S4b+5 Hx) after simple cholecystectomy because of incidental diagnosis of gallbladder cancer and those who underwent simultaneous S4b+5 Hx. A log rank test

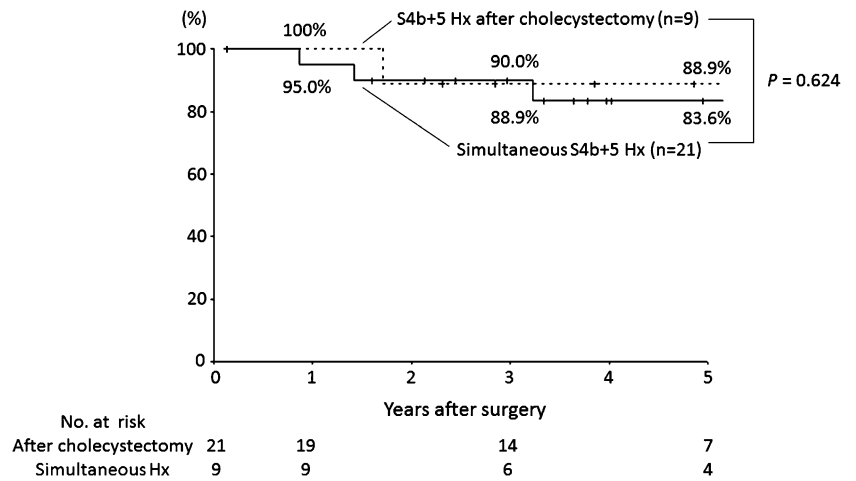


Table 2 Comparison of segment 4b and 5 hepatectomy in multicenter studies

Year:	Our series	JSHPBS 2013	JSBS 2009	JSBS 2009
Pathological TN:	pT2NX (n = 30)	pT2N0 (n = 30)	pT2NX Hepatic-site (n = 58)	pT2NX Peritoneal-site (n = 30)
Age	70.1 ± 8.4	69.5 ± 10.1	64.2 ± 9.5	65.8 ± 10.1
Sex				
Men	8 (27 %)	17 (57 %)	21 (36 %)	8 (27 %)
Bile duct resection	30 (100 %)	16 (53 %)	ND	ND
Operative time (min)	266 ± 62	386 ± 165	ND	ND
Blood loss (ml)	549 ± 312	1156 ± 669	ND	ND
Complication	6 (20 %)	13 (43 %)	8 (14 %)	0
Histological type				
pap	6 (20 %)	14 (46 %)	ND	ND
tub	24 (80 %)	15 (50 %)		
other	0	1 (3 %)		
Lymphovascular and neural invasion				
ly	17 (57 %)	11 (37 %)	ND	ND
v	6 (20 %)	12 (40 %)		
pn	10 (33 %)	6 (20 %)		
Lymph node metastasis	9 (30 %)	0	15 (28 %)	7 (23 %)
Recurrence				
Liver	4 (13 %)	3 (10 %)	2 (3 %)	1 (3 %)
Lymph node	4 (13 %)	2 (7 %)	ND	ND
Peritoneal	2 (7 %)	2 (7 %)	ND	ND
5-year survival	85.1 %	65.9 %	72 %	86 %

Expressed as N (%) except for age, operative time and blood loss (mean ± SD)

JSHPBS The Japanese Society of Hepato-Biliary-Pancreatic Surgery [2], JSBS The Japanese Society of Biliary Surgery [4]

pap Papillary adenocarcinoma, tub Tubular adenocarcinoma, ly Lymphatic invasion, v Vascular invasion, pn Neural invasion

the favorable effect of extrahepatic bile duct resection. One-third of the cases in our series had regional lymph node metastases and perineural invasion. The precise assessment of lymph node metastasis and perineural invasion was limited preoperatively, thereby strongly

suggesting that extrahepatic bile duct resection should be performed in all patients with T2 gallbladder cancers. In several retrospective studies, the authors suggested that strong consideration should be given to resection of the extrahepatic bile duct in patients with T2 gallbladder

cancer, independent of whether resection may affect survival [5, 15, 18]. Choi et al. considered that these insignificant survival differences were perhaps reflected by their selection bias in which more aggressive tumors tended to be addressed with a more aggressive surgical approach including extrahepatic bile duct resection [5]. Thus, surgeons should try to obtain negative margins including the extrahepatic bile duct resection to demonstrate aggressive tumor characteristics [5].

Precise preoperative diagnosis of tumor depth and superficial extension for gallbladder cancers is difficult, when adequate resection is needed, and S4b+5 hepatectomy seems to be a desirable procedure for T2 tumors. A consensus has only been reached regarding the view that prognosis of patients with pT2 gallbladder cancer treated with simple cholecystectomy is poor, and some degree of hepatectomy is necessary for such cases [2]. The patients, who underwent additional S4b+5 hepatectomy after cholecystectomy because of incidental diagnosis of the cancer, also had survival rates comparable to those of patients with simultaneous S4b+5 hepatectomy (Fig. 4). Of note, S4b+5 hepatectomy might prevent early micrometastasis via the cystic vein, especially in hepatic-side tumors because the drainage area of the cystic vein chiefly flows into segment 4b and 5 [4, 19, 20]. In addition, S4b+5 hepatectomy requires correct identification of hepatic S4b and 5 and does not affect liver function excessively [11], whereas keeping precise margins from the tumor may be difficult for liver bed resection, especially in the hepatic hilum. The diagnostic accuracy of preoperative imaging for pT2 was only 33.9 %, and patients with pT2 tumors have a 48.2 % risk of understaging (benign or pT1 tumors) [3]. Although a recent multicentered study showed that tumor location, i.e., hepatic or peritoneal side, affected its survival [6], accurate diagnosis of location is more difficult than determination of depth because it is well known that superficial extension is often detected in biliary tumors [7–10]. Indeed, our results showed that S4b+5 hepatectomy was not affected by tumor location. Therefore, this procedure should be recommended not only for clinical T2 tumors but also for tumors without apparent invasion of surrounding organs. In addition, our surgical results for this procedure support safety and better survival as well as the importance of surgical margin (Fig. 2). Although the clinical results of this procedure have not proven that S4b+5 hepatectomy is superior to gallbladder bed resection [2, 4], S4b+5 hepatectomy would provide accurate and adequate tumor-free margins on the liver side for these tumors.

In conclusion, S4b+5 hepatectomy with extrahepatic bile duct resection could be a good candidate for T2 gallbladder cancers because precise preoperative diagnosis of

tumor depth, location, and lymph node metastasis for these tumors is difficult.

Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflict of interest.

Ethical standard We declare that in the study were respected the ethical standards conformed to the guidelines of the Helsinki Declaration. No study advertising was made and no remuneration was offered.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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